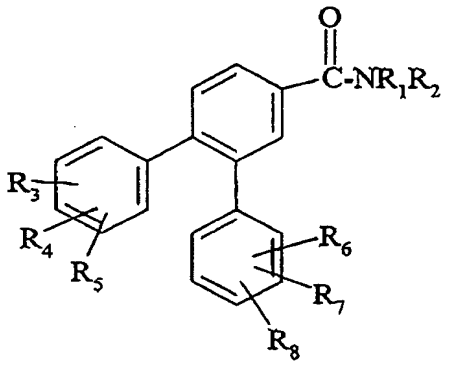
TERPHENYL DERIVATIVES, THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

The present invention relates to terphenyl derivatives, to their preparation and to pharmaceutical compositions comprising them.

Accordingly the present invention provides compounds of formula:



(I)

in which:

- R_1 represents hydrogen or a (C_1-C_4)alkyl;
- R_2 represents: . a (C_3-C_7)alkyl group,
  . an indan-1-yl or 1,2,3,4-tetrahydronaphthalen-1-yl group, said groups being unsubstituted or substituted by a halogen atom and/or a methyl group;
  . a saturated, single-nitrogen heterocyclic radical of 5 to 7 atoms, the nitrogen atom being substituted by a (C_1-C_4)alkyl, benzyl, (C_1-C_3)alkoxycarbonyl or $(C_1-$

C_4)alkanoyl group;

. a group NR_9R_{10};

. a group $(CH_2)_nR_{11}$, $CH(CH_3)R_{11}$, $(CH_2)_mN(CH_3)R_{11}$;

. a C_3-C_{12} nonaromatic carbocyclic radical, unsubstituted or substituted one or more times by a methyl group;

- or R_1 and R_2 together with the nitrogen atom to which they are attached form either a piperazin-1-yl radical substituted in position 4 by a phenyl or benzyl group, or a piperidin-1-yl radical disubstituted in position 4 by a phenyl or benzyl group and by a (C_1-C_4)alkyl or (C_1-C_3)alkanoyl group; the phenyl or benzyl group substituents on the piperazin-1-yl radical or the piperidin-1-yl radical being unsubstituted or substituted by a halogen atom and/or a methyl group;
- R_3, R_4, R_5, R_6, R_7 and R_8 represent each independently of one another a hydrogen or halogen atom or a (C_1-C_6)alkyl, (C_1-C_6)alkoxy or trifluoromethyl group;
- R_9 and R_{10} together with the nitrogen atom to which they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms containing or not containing a second heteroatom selected from O and N, said radical being unsubstituted or

substituted one or more times by a (C_1-C_4)alkyl, hydroxyl or (C_1-C_4)alkoxy group;

- R_{11} represents: . a phenyl which is unsubstituted or substituted by one or more substituents selected from a halogen atom and a methyl group;
  . a heteroaryl radical of 6 to 10 atoms containing one or more nitrogen atoms;
- n represents 1, 2 or 3;
- m represents 0, 2 or 3;

and their salts, their solvates and their hydrates.

The compounds of formula (I) may exist in the form of bases or of addition salts with acids. These salts are advantageously prepared with pharmaceutically acceptable acids, although the salts of other acids useful, for example, for purifying or isolating compounds of formula (I) also form part of the invention.

An alkyl group is a linear or branched radical such as, in particular: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, n-pentyl, isopentyl, n-hexyl or isohexyl, the methyl group being preferred for a (C_1-C_4)alkyl and the *tert*-butyl, 2-methylbut-2-yl and 3,3-dimethylbut-2-yl groups being preferred for a (C_1-C_6)alkyl.

A (C_1-C_6)alkoxy group is a linear or branched

radical containing 1 to 6 carbon atoms, the methoxy group being preferred.

A halogen atom is a fluorine, chlorine, bromine or iodine atom, fluorine, chlorine or bromine atoms being preferred.

The C_3-C_{12} nonaromatic carbocyclic radicals comprise monocyclic or polycyclic, fused or bridged radicals. The monocyclic radicals include cycloalkyls, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, cyclohexyl and cyclopentyl being preferred. The fused dicyclic or tricyclic radicals, bridged or in spiran form, include for example the radicals norbornyl, bornyl, isobornyl, noradamantyl, adamantyl, spiro[5.5]undecanyl and bicyclo[2.2.1]heptanyl, with spiro[5.5]undecanyl and bicyclo[2.2.1]heptanyl being preferred.

A saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom such as O or N, embraces radicals such as morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, 3,6-dihydropyridin-1-yl and octahydrocyclopenta[c]pyrrol-2-yl, preference being given to the radicals pyrrolidin-1-yl, piperidin-1-yl and morpholin-4-yl.

Among the compounds according to the invention preference is given to the compounds of formula (I) in which:

- R_1 represents a hydrogen atom or a (C_1-C_4)alkyl group;
- R_2 represents a group NR_9R_{10} or a nonaromatic C_3-C_{12} carbocyclic radical which is unsubstituted or substituted one or more times by a methyl group;
- R_3, R_4, R_5, R_6, R_7 and R_8 represent each independently of one another a hydrogen or halogen atom or a (C_1-C_6)alkyl, (C_1-C_6)alkoxy or trifluoromethyl group;
- R_9 and R_{10} together with the nitrogen atom to which they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom selected from O and N, said radical being unsubstituted or substituted one or more times by a (C_1-C_6)alkyl group;

and their salts, their solvates and their hydrates.

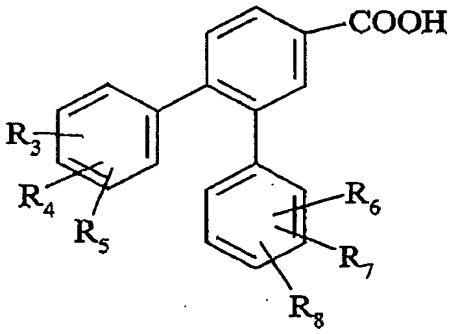
Among the compounds provided by the invention mention may be made of the preferred compounds which are defined by the following values for the substituents:

- R_1 represents a hydrogen atom; and/or
- R_2 represents a group selected from piperidin-1-yl, pyrrolidin-1-yl, cyclohexyl, spiro[5.5]undecanyl and 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl; and/or
- at least one of the substituents R_3, R_4 and R_5

represents a halogen atom or a trifluoromethyl group; and/or

- at least one of the substituents R_6, R_7 and R_8 represents a halogen atom.

The present invention further provides a process for preparing compounds of formula (I). This process is characterized in that a functional derivative of terphenylic acid of formula:



(II)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for (I) is treated with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 are as defined for (I). Optionally the compound thus obtained is converted into one of its salts and/or solvates.

As a functional derivative of the acid (II) it is possible to use the acid chloride, the anhydride, a mixed anhydride, a C_1-C_4 alkyl ester in which the alkyl is linear or branched, an activated ester, for example, the *p*-nitrophenyl ester or the appropriately activated free acid, activated for example with N,N-dicyclohexylcarbodiimide or with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

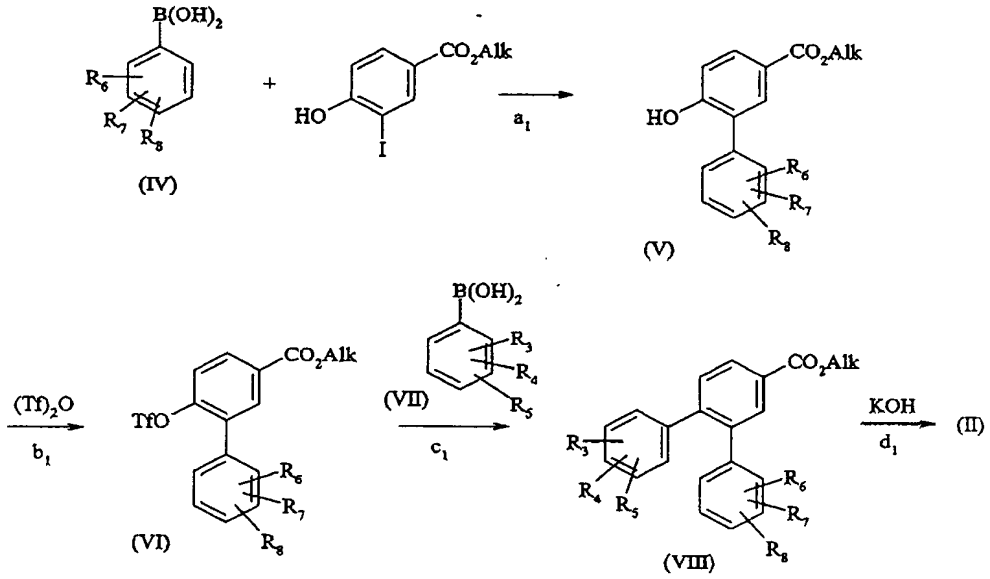
(BOP).

Thus in the process according to the invention the chloride of pyrazol-3-carboxylic acid, obtained by reacting thionyl chloride with the acid of formula (II), can be reacted with an amine HNR_1R_2 in an inert solvent such as a chlorinated solvent (dichloromethane, dichloroethane, or chloroform, for example), an ether (tetrahydrofuran or dioxane, for example) or an amide (N,N-dimethylformamide, for example) under an inert atmosphere at a temperature of between 0°C and the ambient temperature in the presence of a tertiary amine such as triethylamine, N-methylmorpholine or pyridine.

One variant consists in preparing the mixed anhydride of the acid of formula (II) by reacting ethyl chloroformate with the acid of formula (II) in the presence of a base such as triethylamine and in reacting said mixed anhydride with an amine HNR_1R_2 in a solvent such as dichloromethane under an inert atmosphere at ambient temperature in the presence of a base such as triethylamine.

The acids of formula (II) can be prepared in accordance with the following scheme:

SCHEME 1



Alk = (C_1-C_4)alkyl

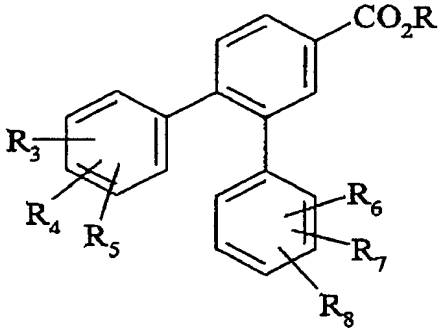
In step a_1 the reaction of the organoborate of formula (IV) with an ester of 4-hydroxy-3-iodobenzoic acid is carried out by the method of Farmaco Ed. Sci., 1958, 13, 121, using the conditions described by Suzuki in Helv. Chem. Acta, 1992, 75, 855.

In step b_1, the product is reacted with triflic anhydride ($(Tf)_2O$) in pyridine in order to prepare the compound of formula (VI). That compound is coupled in step c_1 with an organoborate of formula (VII) under the conditions described in J. Org. Chem., 1992, 57, 379.

The terphenyl ester thus formed is subsequently hydrolyzed by known methods, in the presence of potassium hydroxide, for example, to give the acid of formula (II).

Compounds of formula (II) in which all of the substituents R_3 to R_8 are hydrogen are described in patent US 4,916,145 and in the publication by T. Sato et al., Bull. Chem. Soc. Jap., 1971, 44(9), 2484-2490; the compounds of formula (II) in which the substituents R_3 and R_6 are simultaneously a 3-methoxy, a 4-methoxy or a 3-fluoro, the other substituents R_4, R_5, R_6, R_7 and R_8 being hydrogen, are described in patent US 4,916,145; the compounds of formula (II) in which the substituents R_3, R_4 and R_6, R_7 are simultaneously 3,4-dimethoxy and the substituents R_5 and R_8 are hydrogen are described in the publication by E. Brenna, J. Chem. Soc. Perkin Trans. I, 1998, 901-904.

The other acids of formula (II) and their esters of formula (VIII) are new and constitute a final aspect of the invention. Accordingly, the present invention also provides compounds of formula:



(IIbis)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for (I) and R represents a hydrogen atom or a (C_1-C_4)alkyl group, on condition that R_3, R_4, R_5, R_6, R_7 and R_8 are not simultaneously hydrogen, and on condition that,

when R_4, R_5, R_7 and R_8 represent hydrogen, R_3 and R_6 do not simultaneously represent a fluorine atom in meta position, or a methoxy group in meta or para position, and on condition that when R_5 and R_8 represent hydrogen R_3, R_4 and R_5, R_6 do not simultaneously represent 3,4-dimethoxy groups.

More particularly preference is given to the compounds of formula (IIa) in which:

- R_3 is in position 4 and represents a halogen atom or a trifluoromethyl group;
- R_6 is in position 2 and represents a hydrogen or halogen atom;
- R_7 is in position 4 and represents a halogen atom;
- R_4, R_5 and R_8 are hydrogen.

The amines HNR_1R_2 (III) are known or are prepared by known methods; by way of example mention may be made of: Chem. Ber. 1986, 119, 1413-1423.

The compounds of the formula (I) possess very good *in vitro* affinity ($IC_{50} \leq 10^{-7}$ M) for cannabinoid receptors CB_1, under the experimental conditions described by M. Rinaldi-Carmona et al. (FEBS Letters, 1994, 350, 240-244).

The antagonist nature of the compounds of formula (I) is demonstrated by the results obtained in adenylate cyclase inhibition models as described in M. Rinaldi-Carmona et al., J. Pharmacol. Exp. Ther., 1996, 278, 871-878.

The toxicity of the compounds of formula (I) is compatible with their use as a medicinal product.

In accordance with another of its aspects the present invention provides for the use of a compound of formula (I), or of one of its pharmaceutically acceptable salts, solvates or hydrates, for preparing medicinal products intended for treating diseases involving CB_1 cannabinoid receptors.

For example and without limitation, the compounds of formula (I) are useful as psychotropic medicinal products, particularly for treating psychiatric disorders, including anxiety, depression, mood disorders, insomnia, disorders involving delirium, obsessive disorders, psychoses in general, schizophrenia, and also for treating disorders linked to the use of psychotropic substances, particularly in the case of substance abuse and/or substance addiction, including alcohol addiction and nicotine addiction.

The compounds of formula (I) according to the invention can be used as medicinal products for treating migraine, stress, diseases of psychosomatic origin, panic attacks, epilepsy, locomotor disorders, especially dyskinesias or Parkinson's disease, shaking and dystonia.

The compounds of formula (I) according to the invention can also be used as medicinal products in treating memory disorders, cognitive disorders,

especially in treating senile dementia and Alzheimer's disease, and also in the treatment of attention disorders or vigilance disorders. In addition the compounds of formula (I) may be useful as neuroprotective agents, in treating ischemia and cranial traumas and in treating neurodegenerative diseases, including chorea, Huntingdon's chorea and Tourette's syndrome.

The compounds of formula (I) according to the invention may be used as medicinal products in treating pain: neuropathic pain, peripheral acute pain, and chronic pain of inflammatory origin.

The compounds of formula (I) according to the invention may be used as medicinal products in treating appetite disorders, cravings (for sugars, carbohydrates, drugs, alcohols or any appetizing substance) and/or eating disorders, especially as anorexigenic agents or for treating obesity or bulimia, and also for treating type II diabetes or non-insulin-dependent diabetes. Moreover, the compounds of formula (I) according to the invention may be used as medicinal products in treating gastrointestinal disorders, diarrheic disorders, ulcers, vomiting, urinary and bladder disorders, disorders of endocrine origin, cardiovascular disorders, hypotension, hemorrhagic shock, septic shock, chronic cirrhosis of the liver, asthma, Raynaud's syndrome, glaucoma, fertility

disorders, inflammatory phenomena, immune system diseases, especially autoimmune and neuroinflammatory diseases such as rheumatoid arthritis, reactional arthritis, diseases resulting in demyelinization, multiple sclerosis, infectious and viral diseases such as encephalitis, cerebrovascular accidents, and as medicinal products for anticancer chemotherapy and for treating Guillian-Barré syndrome.

According to the present invention the compounds of formula (I) are especially useful for treating psychotic disorders, especially schizophrenia; for treating appetite disorders and obesity; for treating memory and cognitive disorders; for treating alcohol addiction and nicotine addiction, in other words for alcohol withdrawal and tobacco withdrawal.

According to one of its aspects the present invention relates to the use of a compound of the formula (I), of its pharmaceutically acceptable salts and of their solvates or hydrates for treating the disorders and diseases indicated above.

The compound according to the invention is generally administered as a dosage unit.

Said dosage units are preferably formulated in pharmaceutical compositions in which the active principle is mixed with a pharmaceutical excipient.

Thus, according to another of its aspects, the present invention provides pharmaceutical

compositions comprising as active principle a compound of formula (I), one of its pharmaceutically acceptable salts or one of their solvates.

The compound of formula (I) above and the pharmaceutically acceptable solvates or salts thereof can be used at daily doses of from 0.01 to 100 mg per kg of body weight of the mammal to be treated, preferably at daily doses of from 0.02 to 50 mg/kg. In humans the dose can vary preferably from 0.05 to 4000 mg per day, more particularly from 0.1 to 1000 mg per day, depending on the age of the individual to be treated or on the type of treatment, namely prophylactic or curative. Although these doses are examples of average situations, there may be particular cases where higher or lower doses are appropriate, and such doses also belong to the invention. In accordance with usual practice the dose which is appropriate for each patient is determined by the physician according to the method of administration and the age, weight and response of said patient.

In the pharmaceutical compositions of the present invention for oral, sublingual, inhaled, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle can be administered in unit administration form, as a mixture with conventional pharmaceutical vehicles, to animals and to humans. The suitable unit administration

forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral solutions or suspensions, sublingual and buccal administration forms, aerosols, topical administration forms, implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular administration forms and rectal administration forms.

In the pharmaceutical compositions of the present invention the active principle is generally formulated in dosage units containing from 0.05 to 1000 mg, advantageously from 0.1 to 500 mg, preferably from 1 to 200 mg of said active principle per dosage unit for daily administrations.

In the present description the following abbreviations are used:

DCM: dichloromethane

DMF: dimethylformamide

AcOEt: ethyl acetate

AT: ambient temperature

m.p.: melting point.

The compounds according to the invention are analyzed by LC/UV/MS coupling (liquid chromatography/UV detection/mass spectrometry). Measurements are made of the molecular peak (M^+) and the retention time (t) in minutes.

An Xterra Waters® MS C18 column is used, sold by Waters, measuring 2.1 × 30 mm, 3.5 µm, at ambient

temperature, with a flow rate of 1 mL/minute.

The composition of the eluent is as follows:

- solvent A: 0.025% trifluoroacetic acid (TFA) in water
- solvent B: 0.025% TFA in acetonitrile.

Gradient: the percentage of solvent B varies from 0 to 100% in 2 minutes with a plateau at 100% of B for 1 minute.

UV detection is carried out between 210 nm and 400 nm and mass detection in chemical ionization mode at atmospheric pressure.

For interpreting the nuclear magnetic resonance (NMR) spectra the following abbreviations are used: s: singlet; d: doublet; m: unresolved multiplet; bs: broad singlet; dd: doublet of a doublet.

Preparation 1.1

(IIa): R_3, R_4, R_5 = 4-Cl; R_6, R_7, R_8 = 2,4-diCl.

Methyl 4-2",4"-trichloro[1,1';2',1"]terphenyl-4'-carboxylate.

A) 4-Hydroxy-3-iodobenzoic acid.

30 g of 4-hydroxybenzoic acid are placed in 780 ml of water containing 18 g of sodium hydroxide, 49.5 g of sodium iodide are added, 675 ml of 3.5% sodium hypochlorite solution are run in slowly and the mixture is left with stirring at AT for 13 hours. 60 ml of concentrated H_2SO_4 are added and then, after cooling, the precipitate formed is filtered off and washed with

water. This gives 32.46 g of the expected compound, m.p. = 163°C.

B) Methyl 4-hydroxy-3-iodobenzoate.

32.46 g of the acid obtained in the preceding step is placed in a mixture containing 138 ml of methanol and 10.36 ml of concentrated sulfuric acid and the mixture is heated at reflux for 3 and a half hours. The solvent is concentrated under vacuum and the residue is taken up in demineralized water and ethyl ether. It is neutralized with Na_2CO_3 and then the aqueous phase is extracted with AcOEt. The extract is washed with water and then with a saturated NaCl solution. This gives 32 g of the expected compound.

C) Methyl 2',4'-dichloro-6-hydroxy-(1,1'-biphenyl)-carboxylate.

5.6 g of methyl 4-hydroxy-3-iodobenzoate are introduced under argon into 50 ml of anhydrous DMF and then 4.2 g of 2,4-dichlorophenylboronic acid and 5.54 ml of triethylamine and then 240 mg of tri-*ortho*tolylphosphine are added and the mixture is left under argon for 1 hour. 180 mg of palladium acetate are added and then the mixture is heated at 100°C for 4 hours. 2 g of 2,4-dichlorophenylboronic acid, 5.54 ml of triethylamine, 120 mg of tri-*ortho*tolylphoshine and 180 mg of palladium acetate are added and then the mixture is heated at 100°C for 8 hours. It is concentrated under vacuum and the residue is taken up

in AcOEt and then washed with 10% NH_4OH solution. Extraction is carried out with AcOEt and the extract is washed with water and then with saturated NaCl solution. The residue is dried and then chromatographed on silica, eluting with a cyclohexane/AcOEt mixture (82/18; v/v), to give 3.4 g of the expected compound.

D) Methyl 2',4'-dichloro-6-((trifluoromethyl-sulfonyl)oxy)(1,1'-biphenyl)-3-carboxylate.

3.27 g of the compound obtained in the preceding step are placed in 150 ml of pyridine, the mixture is cooled to between 0°C and 5°C and 2.8 ml of triflic anhydride are run in dropwise. The mixture is maintained with stirring at AT overnight and then concentrated to dryness. The residue is chromatographed on silica, eluting with a cyclohexane/AcOEt mixture (90/10; v/v), to give 3.2 g of the expected compound.

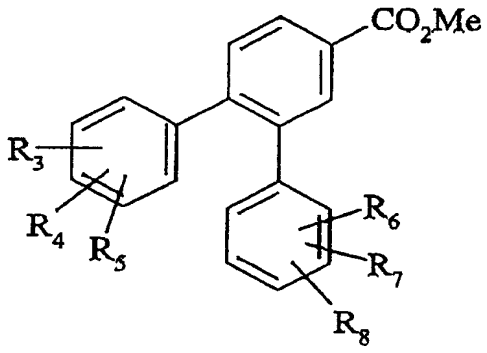
E) Methyl 4,2",4"-trichloro[1,1';2',1"]terphenyl-4'-carboxylate.

3.2 g of the compound obtained in the preceding step are placed in 75 ml of toluene and 2.33 g of 4-chlorophenylboronic acid are added and then 1.55 g of potassium carbonate. The mixture is left under argon for 30 minutes and then 1.38 g of tetrakis(triphenylphosphine)palladium are added and the reaction mixture is heated at between 80°C and 85°C for 3 hours. It is left overnight at AT and then diluted with AcOEt and washed with 5% Na_2CO_3 solution (twice)

and then with saturated NaCl solution. It is dried and then the residue is chromatographed on silica with a cyclohexane/AcOEt mixture (80/20; v/v) to give 1.83 g of the expected compound, which crystallizes from isopropyl ether, m.p. = 136°C.

The procedure described above is used to prepare the methyl esters of the acids of formula (II) collated in the table below.

TABLE 1

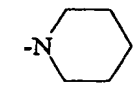


(IIa)

Preparations	R_3, R_4, R_5	R_6, R_7, R_8	m.p.°C/NMR
1.2	4-Cl	4-Cl	223°C
1.3	4-F	2,4-diCl	NMR (DMSO-d_6) δ ppm: 6.9: m: 4H; 7.25: d: 1H; 7.35: dd: 1H; 7.55: m: 2H; 7.80: d: 1H; 8.00: dd: 1H; 13.20: bs: 1H
1.4	4-CF_3	2,4-diCl	206°C

EXAMPLE 1: Compound I

4,2",4"-Trichloro(N-1-piperidinyl)[1,1';2',1"]-terphenyl-4'carboxamide.

(I): R_1 = H; R_2 =  ; R_3, R_4, R_5 = 4-Cl; R_6, R_7,

R_8 = 2,4-diCl

A) 4,2″,4″-Trichloro[1,1′;2′,1″]terphenyl-4′-carboxylic acid.

1.33 g of the compound from Preparation 1.1 is suspended in 30 ml of ethanol, 0.95 g of potassium hydroxide in solution in 5 ml of water is added and the mixture is heated at reflux for 2 hours. After cooling to AT it is filtered over Célite® and concentrated to dryness under vacuum. The residue is taken up in 30 ml of water and then acidified to a pH of 1 by adding 1N HCl. The mixture is cooled using an ice bath and then extracted with AcOEt. It is washed with water and then with saturated NaCl solution to give 1.22 g of the expected compound, m.p. = 237°C.

B) 4,2″,4″-Trichloro[1,1′;2′,1″]terphenyl-4′-carboxylic chloride.

500 mg of the acid obtained in the preceding step are suspended in 50 ml of toluene, 0.3 ml of thionyl chloride is added and the mixture is heated at reflux for 2 hours. The solvent is concentrated twice to give 0.52 g of the expected compound in solid form.

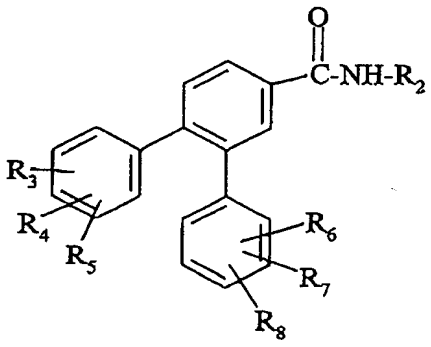
C) 4,2″,4″-Trichloro(N-1-piperidinyl)[1,1′;2′,1″]-terphenyl-4′-carboxamide.

A solution containing 0.17 ml of aminopiperidine and 0.22 ml of triethylamine in 10 ml of DCM is prepared, this solution is cooled to between 0°C and 5°C and 0.52 g of the acid chloride obtained in

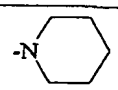
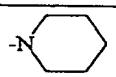
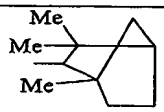
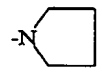
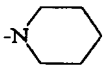
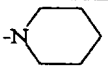
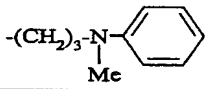
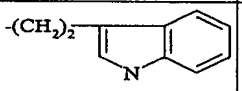
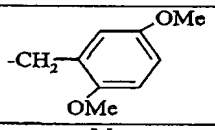
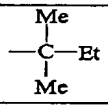
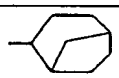
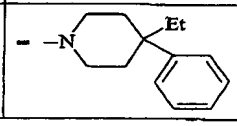
the preceding step in 10 ml of DCM is added dropwise. The mixture is left at +4°C for 2 days. It is poured into ice-water, then extracted with DCM and washed with 5% Na_2CO_3 solution and then with saturated NaCl solution. The extracts are dried and then the residue is chromatographed on silica, eluting with a toluene/AcOEt mixture (88/12; v/v). This gives 0.3 g of the expected compound, m.p. = 182°C.

The procedure of Example 1 is used to prepare the compounds of the invention which are described below.

TABLE 2



(I)

Compounds	R_1	R_2	R_3, R_4, R_5	R_6, R_7, R_8	Characterization
1	H		4-Cl	2,4-diCl	m.p. = 182°C
2	H		4-Cl	4-Cl	m.p. = 233°C
3	H	 (1S) endo	4-Cl	2,4-diCl	m.p. = 98°C
4	H		4-Cl	2,4-diCl	m.p. = 168°C
5	H		4-F	2,4-diCl	m.p. = 175°C
6	H		4-CF_3	2,4-diCl	m.p. = 177°C
7	H		4-Cl	4-Cl	M^+ = 489.49 t = 1.95
8	H		4-Cl	4-Cl	M^+ = 484.95 t = 2.33
9	H		4-Cl	4-Cl	M^+ = 492.15 t = 2.28
10	H		4-Cl	4-Cl	M^+ = 411.98 t = 2.43
11	H		4-Cl	4-Cl	M^+ = 450.50 t = 2.43
12	$-NR_1R_2$		4-Cl	4-Cl	M^+ = 514.42 t = 2.50